Upper Extremity Deep Vein Thrombosis

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Abbreviations

CI	Confidence interval
CT	Computed tomography
CVC	Central venous catheter
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
LMWH	Low-molecular-weight heparin
OR	Odds ratio
PE	Pulmonary embolism
PTS	Post-thrombotic syndrome
TOS	Thoracic outlet syndrome
UEDVT	Upper extremity deep vein thrombosis
UFH	Unfractionated heparin
VCF	Vena cava filter
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

Clinical Pearls

1. Cancer and central venous catheters are the most important risk factors for UEDVT.
2. The risk of PE after UEDVT is estimated 3–12% and is less than with lower extremity DVT estimated at 30%.
3. Central venous catheters that are functioning and needed should not be removed because of UEDVT. Patients should receive anticoagulation as long as the catheter is in situ.

Introduction

Upper extremity deep vein thrombosis (UEDVT) is a disease which was first described in the late nineteenth century by Paget and von Schroetter [1, 2]. The condition accounts for approximately 4–10% of all deep vein thrombosis, with an estimated incidence of 3.6/100,000 patient-years [3]. UEDVT is an increasingly frequent clinical problem, mainly due to the widespread use of central venous catheters (CVCs) which carry a substantial risk of thrombosis [3, 4]. It may involve the radial, ulnar, brachial, axillary, subclavian, internal jugular, and brachiocephalic veins but most often occurs in the subclavian or axillary veins;

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C.I. Ochoa Chaar (ed.), *Current Management of Venous Diseases*,
https://doi.org/10.1007/978-3-319-65226-9_27

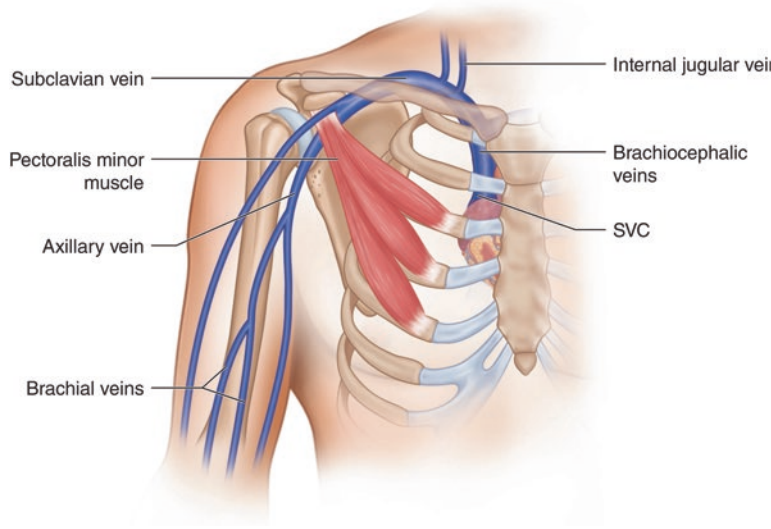


Fig. 27.1 Deep veins that may be involved in upper extremity deep vein thrombosis (SVC, superior vena cava)

frequently more than one venous segment is affected (Fig. 27.1) [5–11]. The cephalic and basilic veins are superficial veins and common site of insertion of peripherally inserted central catheters (PICC). Isolated thrombus in those two veins is not considered UEDVT. Deep vein thrombosis (DVT) of the radial, ulnar, and brachial veins are considered distal UEDVT, whereas DVT in the axillary or more proximally located veins is referred to as proximal UEDVT. As UEDVT may lead to loss of venous access or pulmonary embolism (PE) in the acute phase and is associated with serious long-term complications such as the post-thrombotic syndrome (PTS), prompt diagnosis and treatment are warranted. At present, objective imaging is the cornerstone of diagnosis despite its moderate efficiency. Several strategies to improve diagnostic efficacy have been proposed and tested, but which strategy can most safely and effectively exclude UEDVT remains to be determined.

In the absence of direct evidence, current treatment recommendations are largely extrapolated from studies on lower extremity DVT, since for UEDVT only small, observational studies are available. In this chapter the current understanding on the clinical characteristics, risk factors, diagnosis, management, prognosis, and prevention of UEDVT will be discussed..

Symptoms and Signs

Patients with UEDVT most often present with unilateral swelling and discomfort or localized pain [4, 8, 12–14]. Other symptoms and signs that have been described are weakness, paresthesia, heaviness, low-grade fever, visible collateral veins, erythema, a palpable cord, cyanosis, and warmth (Table 27.1) [8, 12, 16–19]. The majority of UEDVT associated with a CVC or pacemaker remains subclinical, as most cases are discovered during the work-up of a dysfunctional catheter or PE [20–22]. Concomitant symptomatic PE is present in 3–12% of all patients with UEDVT [6, 7, 23–28], which is less than in patients with lower extremity DVT, in which prevalences of around 30% have been reported [23, 28].

Risk Factors

UEDVT is subdivided into primary and secondary UEDVT, based on the pathogenesis. Primary UEDVT represents 20–50% of all cases and includes effort-related thrombosis (also known as the Paget-Schroetter syndrome) in combination with the thoracic outlet syndrome (TOS) and idiopathic thrombosis. The majority of UEDVT is secondary to a predisposing risk factor [3, 9, 29–32].

Table 27.1 Possible symptoms and signs of upper extremity deep vein thrombosis

Symptoms	Prevalence in patients with UEDVT
Unilateral edema or swelling	70–100%[a] [4, 8, 12, 13, 15]
Discomfort or localized pain	34–83%[a] [4, 8, 12, 13, 15]
Weakness	NR
Paresthesia	NR
Heaviness	NR
Signs	
Cyanosis	77% [15]
Warmth	36–52% [12]
Erythema or skin color change	3–47%[a] [4, 13]
Visible collateral veins	20–34%[a] [12]
Palpable cord	3–12%[a] [8]
Low-grade fever	5%[a]
No symptoms or signs	5% [4]

UEDVT upper extremity deep vein thrombosis, *NR* not reported

[a]Including own data from a cohort of 104 consecutive patients with confirmed UEDVT, previously enrolled in a prospective diagnostic management study [7]

The risk factors most strongly associated with UEDVT are cancer and the presence of a CVC. Other risk factors include pacemakers, previous venous thromboembolism (VTE), a positive family history of VTE, arm surgery or trauma, immobilization, the use of estrogens, and thrombophilia (Table 27.2).

The Paget-Schroetter Syndrome

The Paget-Schroetter syndrome accounts for 10–20% of all UEDVT and mainly occurs in young, otherwise healthy individuals who encounter repetitive or strenuous arm movements [10, 32, 38, 39]. It has been mostly associated with sports activities such as baseball, swimming, weight lifting, and wrestling [40, 41] but also with playing the violin for prolonged periods of time. The pathogenesis of the Paget-Schroetter syndrome is not entirely elicited, but it is thought that venous TOS plays a key role. Venous TOS is characterized by compression of the subclavian vein, usually caused by either congenital or acquired variations in the bone and muscle anatomy [42, 43]. This renders the subclavian vein more susceptible to trauma. Repeated trauma then leads to intimal hyperplasia, inflammation, and perivascular fibrosis, which may eventually cause venous thrombosis [44].

Table 27.2 Risk factors for upper extremity deep vein thrombosis

Parameter	Odds ratio (compared to healthy controls)
Cancer	18.1 [29]
Surgery of the upper extremity	13.1 [29]
Central venous catheter	9.7 [4]
Immobilization (plaster cast)	7.0 [29]
Family history of VTE	2.8 [29]
Thrombophilia	2.6–4.2 [29, 33–35]
Trauma of the upper extremity	2.1 [29]
Any surgery lasting more than 1 h	1.7 [36]
Oral contraceptives	1.2–2.9 [29, 34, 37]

VTE venous thromboembolism

Central Venous Catheters

Common indications for CVC placement are the administration of chemotherapy, parenteral nutrition, and prolonged intravenous antibiotic treatment. It is estimated that over 5 million CVCs are inserted annually in the United States [45]. CVC-related UEDVT accounts for up to 70% of all secondary UEDVT [8, 25, 32]. The high risk of CVC-associated UEDVT is mainly due to vessel wall damage following insertion and infusion of irritating substances and to impeded blood flow through the vein across the catheter. The incidence of symptomatic and asymptomatic CVC-related UEDVT lies around 2–6% and 11–19%, respectively [18, 46]. Baseline factors that increase the UEDVT risk are subclavian vein insertion, improper positioning of the catheter tip, and multiple lumen catheters (Table 27.3)

Table 27.3 Central venous catheter-specific risk factors for upper extremity deep vein thrombosis

Parameter	Odds ratio (95% CI)[a]
Type of catheter	
• PICC	1[b]
• Implanted port	0.4 [47]
Number of lumina	
• Single lumen	1[b]
• Double lumen	1.3–7.5 [36, 47, 48]
• Triple lumen	3.3–19.5 [36, 47, 48]
Multiple insertion attempts	1.1[c] [48]
Insertion site	
• Upper arm veins	1[b]
• Subclavian vein	2.2 [47]
• Internal jugular vein	1.6[c] [47]
Catheter tip positioning	
• Proper positioning	1[b]
• Improper positioning	1.9 [47]

CI confidence interval, *PICC* peripherally inserted central catheter
[a]Unadjusted for other risk factors
[b]Reference category
[c]Confidence interval crosses 1

[47]. Peripherally inserted central catheters are associated with a higher UEDVT risk than implanted ports (odds ratio [OR] 2.55, 95% confidence interval [CI] 1.54–3.24), especially in critically ill (incidence 13.9%, 95% CI 7.7–20.1) and cancer patients (incidence 6.7%, 95% CI 4.7–8.6) [47, 48].

Cancer

Approximately 40% of all patients with UEDVT have active cancer; it is one of the strongest risk factors for the development of UEDVT (adjusted OR 18.1, 95% CI 9.4–35.1). The presence of distant metastases increases the risk even further, for an OR of 11.5 (95% CI 1.6–80.2) compared to cancer patients without metastases. Cancer and CVCs often coincide [23], as a substantial proportion of cancer patients require a CVC for the administration of chemotherapy [46]. The presence of a CVC increases the UEDVT risk in patients with active cancer approximately twofold (OR 43.6, 95% CI 25.5–74.6) [29].

Diagnosis

An accurate diagnosis of UEDVT is important, as appropriate treatment can reduce the clinical burden and prevent complications in the acute phase, such as PE. The prevalence of UEDVT in patients with a clinical suspicion of UEDVT varies from 10 to 45% in several cohort studies, which might be explained by differences in study design and the proportions of cancer patients, CVCs, and the number of inpatients (Table 27.4) [7, 12, 49, 50]. In patients with a CVC, the prevalence of UEDVT was 53% in one study [7], compared to only 18% in patients without a CVC ($p < 0.01$). These figures were 31 and 23% for cancer and non-cancer patients, respectively ($p = 0.07$, manuscript under revision).

Venography is the gold standard to diagnose UEDVT, as it visualizes the entire deep vein system of the upper extremity, but it is invasive, expensive, and involves the use of contrast, which may cause complications including renal failure and allergic reactions. Due to these disadvantages, venography has been largely replaced in clinical practice by compression ultrasonography, which is noninvasive, relatively cheap, and easy to perform [19]. In a systematic review, identifying nine studies on the role of compression ultrasonography in the diagnosis of UEDVT, the overall sensitivity was 97% (95% CI 90–100%), with a specificity of 96% (95% CI 87–100%) [51]. The presence of the clavicle may hinder evaluation of the middle part of the subclavian vein, and in case of indeterminate compression ultrasonography results, venography may provide a definitive answer. Other diagnostic options include computed tomography (CT) angiography and magnetic resonance angiography (MRA), which are both noninvasive. However, both have only been evaluated in studies with very few patients with a clinical suspicion of UEDVT, and the diagnostic performance of both modalities is therefore unclear [52, 53].

Several attempts have been made to improve the diagnostic process in patients with a clinical suspicion of UEDVT. Constans and colleagues developed a clinical decision rule, incorporating

Table 27.4 Prevalence of upper extremity deep vein thrombosis and associated risk factors in consecutive patients with a clinical suspicion of upper extremity deep vein thrombosis

	Constans [12]			Armour [7]	Sartori [49, 50]	
	Cohort 1	Cohort 2	Cohort 3		Cohort 1	Cohort 2
Patients, n	140	103	214	406	239	483
UEDVT confirmed, n (%)	50 [42]	46 [51]	65 [31]	103 [26]	24 [10]	64 [13]
Study design	Single center			Multicenter	Single center	
Cancer (%)	52	54	NR	34	16	13
CVC (%)	61	65	12	35	6	17
Inpatient (%)	100	100	53	20	0	0

UEDVT upper extremity deep vein thrombosis, *CVC* central venous catheter, *NR* not reported

Table 27.5 Constans clinical decision score [12]

Item	Count
Venous material present[a]	+1
Localized pain	+1
Unilateral edema	+1
Other diagnosis at least as plausible	−1

If the total score is ≤1, upper extremity deep vein thrombosis is unlikely; if the total score is ≥2, upper extremity deep vein thrombosis is likely

[a]Central venous catheter or pacemaker thread

four items (Table 27.5) [12]. If the total score is one or less, UEDVT is deemed unlikely, whereas if the total score is two or higher, the diagnosis is likely. The prediction of UEDVT based on this score was consistent in three study samples, with prevalences of 64–70% in patients with a total score indicating "UEDVT likely" and 9–13% in those with a total score indicating "UEDVT unlikely," suggesting that this score can be a valuable tool in a diagnostic algorithm [12].

The diagnostic value of D-dimer has been tested in 2 studies, 1 including 52 patients of whom 15 (29%) had UEDVT, and the other including 239 patients of whom 24 (10%) were diagnosed with UEDVT [49, 54]. Both studies applied a cutoff value of 500 ng/mL. The sensitivity was high in both studies with 100% (95% CI 78–100%) and 92% (95% CI 73–99%), respectively, whereas the specificity was low (14%, 95% CI 4–29% and 60%, 95% CI 52–67%, respectively). These figures were similar for cancer patients and patients with a CVC [49, 54].

Recently, a multicenter, international, prospective diagnostic management study evaluated an algorithm consisting of the Constans score, D-dimer testing, and compression ultrasonography in consecutive patients with a clinical suspicion of UEDVT [7]. In total, 406 patients were included, and the algorithm was feasible in 390 (96%). UEDVT was confirmed in 103 patients (25%). In 87 patients (21%; 95% CI 17–25%), ultrasonography could be withheld. One patient, in which UEDVT was initially excluded, developed a UEDVT during 3-month follow-up, for an overall failure rate of the algorithm of 0.4% (95% CI 0–2.2%). In another study, 483 patients with a clinical suspicion of UEDVT all underwent immediate compression ultrasonography and were followed for 3 months prospectively. The failure rate, defined as the rate of recurrent VTE, was 0.6% (95% CI 0.2–2.2%) for single ultrasonography and 0.2% (95% CI 0.1–1.7%) for serial ultrasonography. Of note, the prevalence of UEDVT was relatively low in this cohort (13%) [50].

While there have been important improvements in the field, the best diagnostic strategy in patients with a clinical suspicion of UEDVT remains to be determined. Hence, at present, objective imaging remains the cornerstone of UEDVT diagnosis. D-dimer testing may help to reduce the number of patients who require imaging, although the efficiency of the test appears moderate in this population with high prevalences of cancer and CVCs. The use of an algorithm has been shown to be efficient and safe but

needs to be validated prospectively before it can be implemented in clinical practice. Furthermore, improvement of the algorithm appears to be desirable, for example, by applying age-adjusted D-dimer cutoff values (van Es, in press). In patients with a CVC and a suspicion of UEDVT, direct imaging seems justified, as only two examinations must be performed to detect one UEDVT.

Treatment

In the acute phase of UEDVT, the goal is to relieve acute symptoms and prevent complications, such as the loss of venous access or development of PE. The long-term goals of treatment are mainly the prevention of recurrent VTE, including fatal PE, and the development of PTS. Treatment of UEDVT is based on anticoagulation predominantly with selective use of thrombolytic therapy, mechanical catheter interventions, first rib resection, and vena cava filter (VCF) placement. No randomized controlled trials have evaluated any of these therapies in patients with UEDVT. Therefore, treatment recommendations by the major guidelines are largely extrapolated from studies on DVT of the leg and are only based on small observational studies in UEDVT patients [55].

Anticoagulant Therapy

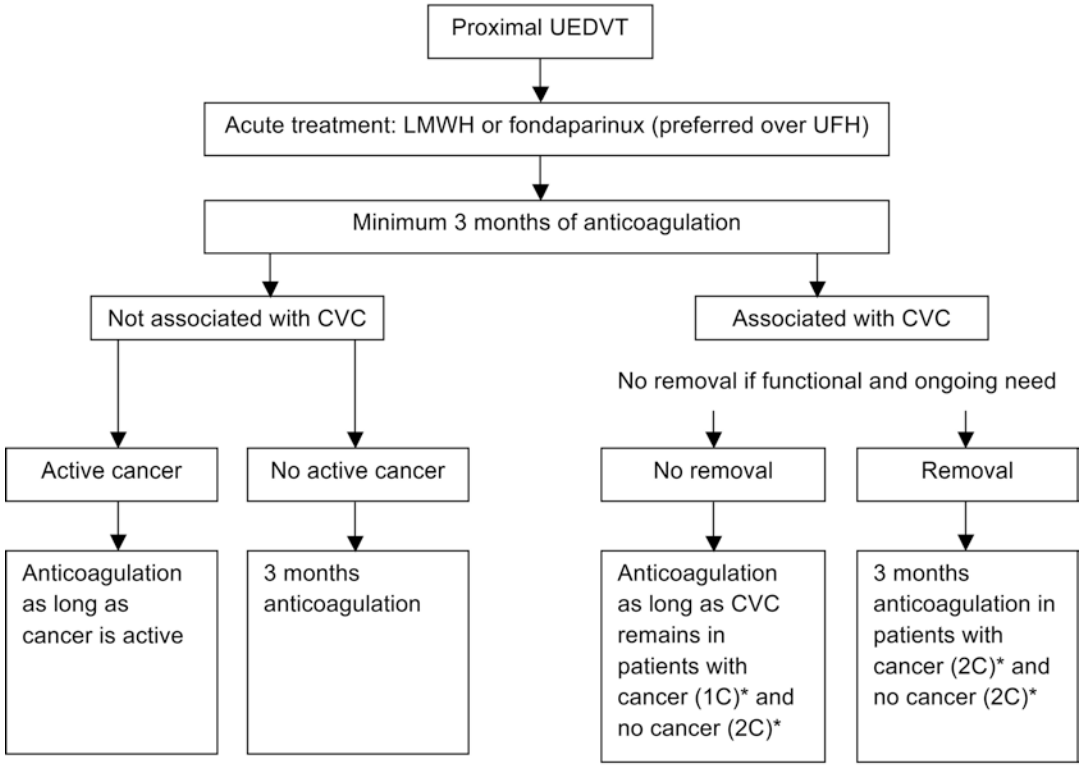
In patients with lower extremity DVT, low-molecular-weight heparin (LMWH) has a superior efficacy and better safety compared to unfractionated heparin (UFH) for the initial period of treatment (i.e., the first 5–10 days) [56]. In addition, 4 observational studies that included a total of 209 patients with UEDVT receiving LMWH reported low recurrence and major bleeding rates [27, 57–59]. Based on these data, LMWH is the preferred anticoagulant for the initial phase of UEDVT treatment (Fig. 27.2). UFH is reserved for patients with contraindications to LMWH such as severe renal failure [55].

For the long-term treatment of UEDVT, i.e., after the initial phase of 5–10 days, treatment options besides LMWH are vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs). VKA have been the standard method of anticoagulation for decades, but the use of DOACs is emerging since large trials have shown that they are as effective as VKA for the treatment of acute symptomatic lower extremity DVT and PE, with a significant reduction in major bleeding events [60]. Extrapolating from trials investigating these drugs for the treatment of DVT of the leg or PE, both can be considered for long-term UEDVT treatment. LMWH may be prescribed, but the daily injections are cumbersome and painful for many patients, and hypersensitivity skin reactions are often seen. Despite these disadvantages, the cornerstone of treatment in cancer patients is LMWH, based on a superior efficacy and similar safety profile compared to VKA in cancer patients with lower extremity DVT and PE [61, 62].

Treatment Duration

All patients with proximal UEDVT (i.e., DVT of the axillary or more proximally located veins) are recommended to be treated with a therapeutic dose of anticoagulants for at least 3 months (Fig. 27.2). If UEDVT is not associated with a CVC but is associated with active cancer, patients should receive anticoagulation as long as cancer is active or the patient is receiving chemotherapy. In non-cancer patients with non-CVC-associated UEDVT, 3 months of treatment is recommended.

If the UEDVT is CVC associated, the CVC should not be removed if it is functioning well and there is an ongoing need for it. This recommendation is in part based on the fact that many patients still require central venous access and insertion of another CVC will increase the thrombotic risk as well. Furthermore, an observational study showed no benefit of CVC removal in 58 of 112 patients (52%) with symptomatic CVC-related thrombosis. In total, four patients failed to show resolution of their presenting symptoms, all of whom had their CVC removed at the time of UEDVT [63]. In another, prospective study including 74 patients with acute symptomatic



UEDVT: upper extremity deep vein thrombosis; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; CVC: central venous catheter
* Grading of Recommendations Assessment, Development and Evaluation (GRADE); 1C: strong recommendation based on low-quality evidence, 2C: weak recommendation based on low-quality evidence

Fig. 27.2 Treatment recommendations for upper extremity deep vein thrombosis [55]

CVC-related UEDVT in which the catheter remained in place, there were no recurrent VTE during 3 months of anticoagulant therapy [57]. According to the ACCP guideline, anticoagulation should be given as long as the CVC remains in place. This is similar for cancer and non-cancer patients. If the CVC is removed, only 3 months of treatment is recommended, regardless of the presence of cancer. There are no data to guide whether CVC removal should be preceded by anticoagulant therapy [55]. There is some debate on the safety of cessation of therapy in patients in whom the CVC is removed but who still have active cancer after 3 months. In a recent retrospective study, the cumulative probability of recurrent VTE was 22.2% in patients with active cancer after cessation of anticoagulant therapy, compared to 2.3% in those in remission ($p = 0.02$) [64]. Another study reported a recurrent VTE rate after 3 months of 7.7% in cancer patients with CVC-related UEDVT, compared to 4.4% in cancer patients with non-CVC-related UEDVT [23]. These data suggest that patients with active cancer with CVC-related UEDVT in whom the CVC is removed may benefit from anticoagulation beyond 3 months.

For distal UEDVT, there is significant uncertainty on the benefits of anticoagulation, as it is thought that complications occur less often and are less severe in case of distal UEDVT as compared to proximal UEDVT. Therefore, conservative treatment with close surveillance to detect UEDVT

extension, a prophylactic dose of anticoagulation, or a shorter course of treatment are options alternative to full therapeutic anticoagulation. If distal UEDVT is symptomatic, associated with a CVC (with the CVC remaining in situ) or with cancer, 3 months of therapeutic dose anticoagulation is favored, unless there is a high bleeding risk [55].

Thrombolytic Therapy

Thrombolytic therapy may improve early and late venous patency in patients with UEDVT [65–69], but whether it lowers the risk of recurrent VTE or development of PTS remains unknown. The American College of Chest Physicians (ACCP) guideline suggests that thrombolysis is considered only in patients with severe symptoms for less than 14 days with a good functional status, a life expectancy of at least 1 year, and a low risk of bleeding [55]. Data on the use of thrombolytic therapy for UEDVT is limited but suggests a high risk of major bleeding of up to 17% when systemically administered [66, 68, 69]. Therefore, if thrombolysis is applied, catheter-directed thrombolysis is recommended over systemic thrombolysis, based on the assumption that this is associated with lower bleeding risk [55].

Mechanical Catheter Interventions

Mechanical interventions include clot aspiration, fragmentation, thrombectomy, percutaneous transluminal angioplasty, and stent placement. These techniques are mostly used in combination with catheter-directed thrombolysis. Stents have been associated with high rates of complications such as stent fracture and rethrombosis in the presence of TOS [70, 71].

First Rib Resection

In patients with UEDVT and TOS, surgical decompression through first rib resection has been advocated [55]. No randomized trials have evaluated the efficacy and safety of first rib resection in the resolution of acute complaints and prevention of long-term sequelae such a recurrent VTE and PTS. The indications for first rib resection will be discussed in a separate chapter.

Vena Cava Filter

In patients with a contraindication for anticoagulant therapy, placement of a VCF may be considered. In a review, reporting on a total of 209 superior VCF placements in patients with UEDVT, complications occurred in 3.8% of the cases, including cardiac tamponade, aortic perforations, and a pneumothorax [72]. The use of VCF should be limited to experienced centers in selected cases.

Other Therapies

The use of compression stockings to prevent PTS after UEDVT has not been investigated, and the ACCP suggests against its routine use [55].

Prognosis

On the long term, UEDVT can be complicated by recurrent VTE, PTS, bleeding during anticoagulation, and death. To date, mostly small studies with methodological shortcomings have evaluated the long-term clinical outcome of UEDVT. A systematic review of all available studies on this topic reported an average incidence of recurrent VTE of 3–4% during anticoagulant therapy. After cessation of treatment, the annual incidence of recurrence lies around 4% [73]. PTS after UEDVT seems to occur infrequently, and complaints are mostly mild [32, 74]. Compared to DVT of the leg, the incidences of recurrent VTE and of PTS after UEDVT seem relatively low [27, 28, 32, 74, 75].

The recurrence risk in patients with CVC-related UEDVT was reported in two prospective studies; one observed an incidence of 7 per 100 patient-years during anticoagulant therapy, which decreased to 3.4 per 100 patient-years after cessation of treatment [76]. Another study observed recurrent VTE in 4.4% of the patients during

3 months of anticoagulant therapy [23]. Of note, in both studies no information was available on catheter removal. Cancer patients with UEDVT appear to have a twofold higher risk of recurrent VTE compared to non-cancer patients [23, 32, 73], which is comparable to findings from studies on DVT of the leg or PE [77, 78].

In patients receiving a therapeutic dose of anticoagulants, the cumulative incidence of major bleeding is approximately 4% after half a year of treatment [23, 32, 59, 73, 79]. The mortality rate in patients with UEDVT is high and reflects the high prevalence of underlying cancer. To which extent fatal PE adds to this risk is unclear.

Prevention

The prevention of UEDVT has mainly been investigated in patients with indwelling CVCs. A total of six meta-analyses evaluating the efficacy and safety of VKA in the prevention of CVC-related thrombosis showed no overall benefit on the occurrence of symptomatic thrombosis compared to placebo or no treatment [80]. Six randomized studies in cancer patients with CVCs found no increased risk of bleeding with LMWH thromboprophylaxis but also no benefit in preventing CVC-related thrombosis. Routine anticoagulant thromboprophylaxis is therefore not recommended in patients with a CVC by the major international guidelines [55, 80]. The role of UFH, thrombolytics, and heparin-bonded catheters in the prevention of CVC-related thrombosis remains uncertain [47, 80]. CVCs should only be placed in carefully selected patients in whom the benefits outweigh the risks. As mentioned before, several catheter-specific factors increase the risk of UEDVT and should be taken into account when placing a CVC (Table 27.3).

Future Directions

Several aspects related to UEDVT remain unresolved. Future studies need to evaluate what the most effective and safe diagnostic strategy is to confirm or refute UEDVT. Furthermore, in cancer patients with CVC-related UEDVT in whom the CVC is removed, the efficacy and safety of 3 months of anticoagulant therapy versus prolonged treatment should be assessed. Ideally, future studies would include the use of DOACs for the treatment of UEDVT.

More research is warranted to identify those patients with a CVC in whom the benefits of pharmacological thromboprophylaxis exceed the associated harms, for example, by risk stratification. Also, new regimens that are possibly effective and safe in preventing CVC-associated UEDVT, including prophylactic doses of DOACs, should be explored.

Acknowledgments We would like to acknowledge Marcello Di Nisio for his critical revision of the manuscript for intellectual content.

References

1. Paget J. Clinical lectures and essays, vol. 466. Harlow: Longmen Green; 1875.
2. von Schroetter L. Erkrankungen der Gefasse. In:Nathnagel Handb der Pathol und Ther Anon. Wein: Holder; 1884. p. 533–5.
3. Isma N, Svensson PJ, Gottsäter A, Lindblad B. Upper extremity deep venous thrombosis in the population-based Malmö thrombophilia study (MATS). Epidemiology, risk factors, recurrence risk, and mortality. Thromb Res. 2010;125(6):e335–8.
4. Joffe HV, Kucher N, Tapson VF, Goldhaber SZ. Upper-extremity deep vein thrombosis: a prospective registry of 592 patients. Circulation. 2004;110(12):1605–11.
5. Prandoni P, Bernardi E. Upper extremity deep vein thrombosis. Curr Opin Pulm Med. 1999;5(4):222–6.
6. Hingorani A, Ascher E, Lorenson E, DePippo P, Salles-Cunha S, Scheinman M, et al. Upper extremity deep venous thrombosis and its impact on morbidity and mortality rates in a hospital-based population. J Vasc Surg. 1997;26(5):853–60.
7. Kleinjan A, Di Nisio M, Beyer-Westendorf J, Camporese G, Cosmi B, Ghirarduzzi A, et al. Safety and feasibility of a diagnostic algorithm combining clinical probability, d-dimer testing, and ultrasonography for suspected upper extremity deep venous thrombosis: a prospective management study. Ann Intern Med. 2014;160(7):451–7.
8. Marinella MA, Kathula SK, Markert RJ. Spectrum of upper-extremity deep venous thrombosis in a community teaching hospital. Heart Lung. 2000;29(2):113–7.
9. Linnemann B, Meister F, Schwonberg J, Schindewolf M, Zgouras D, Lindhoff-Last E, et al. Hereditary and acquired thrombophilia in patients with upper extremity deep-vein thrombosis. Results

from the MAISTHRO registry. Thromb Haemost. 2008;100(3):440–6.
10. Prandoni P, Polistena P, Bernardi E, Cogo A, Casara D, Verlato F, et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med. 1997;157(1):57–62.
11. Hingorani A, Ascher E, Hanson J, Scheinman M, Yorkovich W, Lorenson E, et al. Upper extremity versus lower extremity deep venous thrombosis. Am J Surg. 1997;174(97):214–7.
12. Constans J, Salmi L-R, Sevestre-Pietri M-A, Perusat S, Nguon M, Degeilh M, et al. A clinical prediction score for upper extremity deep venous thrombosis. Thromb Haemost. 2008;99(1):202–7.
13. Mustafa S, Stein PD, Patel KC, Otten TR, Holmes R, Silbergleit A. Upper extremity deep venous thrombosis. Chest. 2003;123(6):1953–6.
14. Urschel HC, Razzuk MA. Improved management of the Paget-Schroetter syndrome secondary to thoracic outlet compression. Ann Thorac Surg. 1991;52(6):1217–21.
15. Urschel HC, Razzuk MA. Paget-Schroetter syndrome: what is the best management? Ann Thorac Surg. 2000;69(6):1663–8.
16. Joffe HV, Goldhaber SZ. Upper-extremity deep vein thrombosis. Circulation. 2002;106(14):1874–80.
17. Bernardi E, Pesavento R, Prandoni P. Upper extremity deep venous thrombosis. Semin Thromb Hemost. 2006;32(7):729–36.
18. Grant JD, Stevens SM, Woller SC, Lee EW, Kee ST, Liu DM, et al. Diagnosis and management of upper extremity deep-vein thrombosis in adults. Thromb Haemost. 2012;108(6):1097–108.
19. Kucher N. Clinical practice. Deep-vein thrombosis of the upper extremities. N Engl J Med. 2011;364(9):861–9.
20. Akl EA, Kamath G, Yosuico V, Kim SY, Barba M, Sperati F, et al. Thromboprophylaxis for patients with cancer and central venous catheters: a systematic review and a meta-analysis. Cancer. 2008;112(11):2483–92.
21. van Rooden CJ, Molhoek SG, Rosendaal FR, Schalij MJ, Meinders AE, Huisman MV. Incidence and risk factors of early venous thrombosis associated with permanent pacemaker leads. J Cardiovasc Electrophysiol. 2004;15(11):1258–62.
22. Van Rooden CJ, Rosendaal FR, Meinders AE, Van Oostayen JA, Van Der Meer FJM, Huisman MV. The contribution of factor V Leiden and prothrombin G20210A mutation to the risk of central venous catheter-related thrombosis. Haematologica. 2004;89(2):201–6.
23. Muñoz FJ, Mismetti P, Poggio R, Valle R, Barrón M, Guil M, et al. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE registry. Chest. 2008;133(1):143–8.
24. Horattas MC, Wright DJ, Fenton AH, Evans DM, Oddi MA, Kamienski RW, et al. Changing concepts of deep venous thrombosis of the upper extremity–report of a series and review of the literature. Surgery. 1988;104(3):561–7.
25. Kooij JDB, Van Der Zant FM, Van Beek EJR, Reekers JA. Pulmonary embolism in deep venous thrombosis of the upper extremity: more often in catheter-related thrombosis. Neth J Med. 1997;50:238–42.
26. Kerr TM, Lutter KS, Moeller DM, Hasselfeld KA, Roedersheimer R, McKenna PJ, et al. Upper extremity venous thrombosis diagnosed by duplex scanning. Am J Surg. 1990;160(2):202–6.
27. Prandoni P, Bernardi E, Marchiori A, Lensing AWA, Prins MH, Villalta S, et al. The long term clinical course of acute deep vein thrombosis of the arm: prospective cohort study. BMJ. 2004;329(7464):484–5.
28. Lechner D, Wiener C, Weltermann A, Eischer L, Eichinger S, Kyrle PA. Comparison between idiopathic deep vein thrombosis of the upper and lower extremity regarding risk factors and recurrence. J Thromb Haemost. 2008;6(8):1269–74.
29. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Old and new risk factors for upper extremity deep venous thrombosis. J Thromb Haemost. 2005;3(11):2471–8.
30. Spaander MCW, Hoekstra J, Hansen BE, Van Buuren HR, Leebeek FWG, Janssen HLA. Anticoagulant therapy in patients with non-cirrhotic portal vein thrombosis: effect on new thrombotic events and gastrointestinal bleeding. J Thromb Haemost. 2013;11(3):452–9.
31. Leebeek FW, Stadhouders NA, van Stein D, Gómez-García EB, Kappers-Klunne MC. Hypercoagulability states in upper-extremity deep venous thrombosis. Am J Hematol. 2001;67(1):15–9.
32. Bleker SM, van Es N, Kleinjan A, Büller HR, Kamphuisen PW, Aggarwal A, et al. Current management strategies and long-term clinical outcomes of upper extremity venous thrombosis. J Thromb Haemost. 2016;14(5):973–81.
33. Martinelli I, Cattaneo M, Panzeri D, Taioli E, Mannucci PM. Risk factors for deep venous thrombosis of the upper extremities. Ann Int Med. 1997;126(9):707–11.
34. Martinelli I, Battaglioli T, Bucciarelli P, Passamonti SM, Mannuccio PM. Risk factors and recurrence rate of primary deep vein thrombosis of the upper extremities. Circulation. 2004;110(5):566–70.
35. Bombeli T, Basic A, Fehr J. Prevalence of hereditary thrombophilia in patients with thrombosis in different venous systems. Am J Hematol. 2002;70(2):126–32.
36. Evans RS, Sharp JH, Linford LH, Lloyd JF, Tripp JS, Jones JP, et al. Risk of symptomatic DVT associated with peripherally inserted central catheters. Chest. 2010;138(4):803–10.
37. Vayá A, Mira Y, Mateo J, Falco C, Villa P, Estelles A, et al. Prothrombin G20210A mutation and oral contraceptive use increase upper-extremity deep vein thrombotic risk. Thromb Haemost. 2003;89(3):452–7.
38. Lindblad B, Tengborn L, Bergqvist D. Deep vein thrombosis of the axillary-subclavian veins: epidemiologic data, effects of different types of treatment and late sequelae. Eur J Vasc Surg. 1988;2(3):161–5.
39. Sajid MS, Ahmed N, Desai M, Baker D, Hamilton G. Upper limb deep vein thrombosis: a literature

review to streamline the protocol for management. Acta Haematol. 2007;118(1):10–8.
40. Zell L, Kindermann W, Marschall F, Scheffler P, Gross J, Buchter A. Paget-Schroetter syndrome in sports activities—case study and literature review. Angiology. 2001;52(5):337–42.
41. van Stralen KJ, Blom JW, Doggen CJM, Rosendaal FR. Strenuous sport activities involving the upper extremities increase the risk of venous thrombosis of the arm. J Thromb Haemost. 2005;3(9):2110–1.
42. Illig KA, Doyle AJ. A comprehensive review of paget-schroetter syndrome. J Vasc Surg. 2010;51(6):1538–47.
43. Sanders RJ, Hammond SL, Rao NM. Diagnosis of thoracic outlet syndrome. J Vasc Surg. 2007;46(3):601–4.
44. Alla VM, Natarajan N, Kaushik M, Warrier R, Nair CK. Paget-schroetter syndrome: review of pathogenesis and treatment of effort thrombosis. West J Emerg Med. 2010;11(4):358–62.
45. McGee DC, Gould MK. Preventing complications of central venous catheterization. N Engl J Med. 2003;348(12):1123–33.
46. Shivakumar SP, Anderson DR, Couban S. Catheter-associated thrombosis in patients with malignancy. J Clin Oncol. 2009;27(29):4858–64.
47. Lee AYY, Kamphuisen PW. Epidemiology and prevention of catheter-related thrombosis in patients with cancer. J Thromb Haemost. 2012;10(8):1491–9.
48. Chopra V, Anand S, Hickner A, Buist M, Rogers MA, Saint S, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. Lancet. 2013;382(9889):311–25.
49. Sartori M, Migliaccio L, Favaretto E, Cini M, Legnani C, Palareti G, et al. D-dimer for the diagnosis of upper extremity deep and superficial venous thrombosis. Thromb Res. 2015;135(4):673–8.
50. Sartori M, Migliaccio L, Favaretto E, Brusi C, Conti E, Rodorigo G, et al. Whole-arm ultrasound to rule out suspected upper-extremity deep venous thrombosis in outpatients. JAMA Intern Med. 2015;175(7):1226–7.
51. Di Nisio M, Van Sluis GL, Bossuyt PMM, Büller HR, Porreca E, Rutjes AWS. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. J Thromb Haemost. 2010;8(4):684–92.
52. Baarslag HJ, Van Beek EJR, Reekers JA. Magnetic resonance venography in consecutive patients with suspected deep vein thrombosis of the upper extremity: initial experience. Acta Radiol. 2004;45(1):38–43.
53. Kim H-C, Chung JW, Park JH, Yin YH, Park SH, Yoon CJ, et al. Role of CT venography in the diagnosis and treatment of benign thoracic central venous obstruction. Korean J Radiol. 2003;4(3):146–52.
54. Merminod T, Pellicciotta S, Bounameaux H. Limited usefulness of D-dimer in suspected deep vein thrombosis of the upper extremities. Blood Coagul Fibrinolysis. 2006;17(3):225–6.
55. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S–94S.
56. van Dongen CJJ, van den Belt AGM, Prins MH, Lensing AWA. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev. 2004;4:CD001100.
57. Kovacs MJ, Kahn SR, Rodger M, Anderson DR, Andreou R, Mangel JE, et al. A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (the catheter study). J Thromb Haemost. 2007;5(8):1650–3.
58. Karabay O, Yetkin U, Onol H. Upper extremity deep vein thrombosis: clinical and treatment characteristics. J Int Med Res. 2004;32(4):429–35.
59. Savage KJ, Wells PS, Schulz V, Goudie D, Morrow B, Cruickshank M, et al. Outpatient use of low molecular weight heparin (dalteparin) for the treatment of deep vein thrombosis of the upper extremity. Thromb Haemost. 1999;82(3):1008–10.
60. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood. 2014;124(12):1968–75.
61. Akl EA, Kahale L, Barba M, Neumann I, Labedi N, Terrenato I, et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer (review). Cochrane Database Syst Rev. 2014;10:CD006468.
62. van Es N, Bleker SM, Wilts IT, Porreca E, Di Nisio M. Prevention and treatment of venous thromboembolism in patients with cancer: focus on drug therapy. Drugs. 2016;76(3):331–41.
63. Frank DA, Meuse J, Hirsch D, Ibrahim JG, van den Abbeele AD. The treatment and outcome of cancer patients with thromboses on central venous catheters. J Thromb Thrombolysis. 2000;10(3):271–5.
64. Delluc A, Le Gal G, Scarvelis D, Carrier M. Outcome of central venous catheter associated upper extremity deep vein thrombosis in cancer patients. Thromb Res. 2014;135(2):298–302.
65. Sabeti S, Schillinger M, Mlekusch W, Haumer M, Ahmadi R, Minar E. Treatment of subclavian-axillary vein thrombosis: long-term outcome of anticoagulation versus systemic thrombolysis. Thromb Res. 2002;108(5–6):279–85.
66. Vik A, Holme P, Singh K, Dorenberg E, Nordhus K, Kumar S, et al. Catheter-directed thrombolysis for treatment of deep venous thrombosis in the upper extremities. Cardiovasc Interv Radiol. 2009;32(5):980–7.
67. AbuRahma AF, Short YS, White JF, Boland JP. Treatment alternatives for axillary-subclavian vein thrombosis: long-term follow-up. Cardiovasc Surg. 1996;4(6):783–7.

68. Seigel EL, Jew AC, Delcore R, Iliopoulos JI, Thomas JH. Thrombolytic therapy for catheter-related thrombosis. Am J Surg. 1993;166(6):716–8.
69. Kreienberg PB, Chang BB, Darling RC, Roddy SP, Paty PS, Lloyd WE, et al. Long-term results in patients treated with thrombolysis, thoracic inlet decompression, and subclavian vein stenting for Paget-Schroetter syndrome. J Vasc Surg. 2001;33(2 Suppl):S100–5.
70. Meier GH, Pollak JS, Rosenblatt M, Dickey KW, Gusberg RJ, Druy EM, et al. Initial experience with venous stents in exertional axillary-subclavian vein thrombosis. J Vasc Surg. 1996;24(6):974–83.
71. Urschel HC, Patel AN. Paget-Schroetter syndrome therapy: failure of intravenous stents. Ann Thorac Surg. 2003;75(6):1693–6.
72. Owens CA, Bui JT, Knuttinen MG, Gaba RC, Carrillo TC. Pulmonary embolism from upper extremity deep vein thrombosis and the role of superior vena cava filters: a review of the literature. J Vasc Interv Radiol. 2010;21(6):779–87.
73. Bleker SM, van Es N, van Gils L, Daams JG, Kleinjan A, Büller HR, et al. Clinical course of upper extremity deep vein thrombosis in patients with or without cancer: a systematic review. Thromb Res. 2016;140(Suppl):S81–8.
74. Elman EE, Kahn SR. The post-thrombotic syndrome after upper extremity deep venous thrombosis in adults: a systematic review. Thromb Res. 2006;117(6):609–14.
75. Kahn SR, Elman EA, Bornais C, Blostein M, Wells PS. Post-thrombotic syndrome, functional disability and quality of life after upper extremity deep venous thrombosis in adults. Thromb Haemost. 2005;93(3):499–502.
76. Baumann Kreuziger L, Cote L, Verhamme P, Greenberg S, Caprini J, Muñoz F, et al. A RIETE registry analysis of recurrent thromboembolism and hemorrhage in patients with catheter-related thrombosis. J Vasc Surg Venous Lym Dis. 2015;3(3):243–50.
77. Prandoni P, Lensing AWA, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100(10):3484–8.
78. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Büller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol. 2000;18(17):3078–83.
79. Rathbun SW, Stoner JA, Whitsett TL. Treatment of upper-extremity deep vein thrombosis. J Thromb Haemost. 2011;9(10):1924–30.
80. Debourdeau P, Farge D, Beckers M, Baglin C, Bauersachs RM, Brenner B, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. J Thromb Haemost. 2013;11(1):71–80.